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Subject: TSCA Section 8(d): Reporting of Health and Safety Information

Ladies and Gentlemen:

BASF Corporation is hereby submitting the final report of a Health and Safety study carried out with Toluene Diisocyanate (TDI) (CAS No. 584-84-9). Please refer to original notification sent January 10, 1997.

Chemical Substance:	Toluene diisocyanate
CAS Registry #:	584-84-9
Submitting Site:	BASF Corporation 3000 Continental Drive North Mt. Olive, NJ 07828-1234
Submitting Official:	Teddi Konas Product Stewardship & Product Safety Team Member BASF Corporation 1609 Biddle Avenue Wyandotte, MI 48192

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A 04

Respiratory health surveillance in a toluene diisocyanate production unit, 1967-97 – Clinical observations and lung function analyses

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A 05

Respiratory health surveillance in a toluene diisocyanate production unit, 1967-97 – Clinical observations and lung function analyses

ABSTRACT

Objectives: - To characterize irritant and allergic airway responses and assess changes in FVC and FEV_1 in relation to toluene diisocyanate (TDI) exposure.

Methods: - Employees (N=313) ever assigned to a TDI production unit for 3+ months (1967-1992) were identified from personnel records along with 158 frequency-matched referents without known TDI exposure. Occupational clinic visit reports of TDI-related exposure incidents and annual periodic examination results (questionnaire, physical findings and spirometry) were abstracted and assessed relative to industrial hygiene estimates of TDI exposure.

Results: - Mean 8-hour time-weighted average estimates of TDI concentrations ranged from 9.9 parts-per-billion (ppb) in high potential exposure jobs during the early years of plant operations to 0.5 ppb in low potential exposure jobs in more recent years. The corresponding clinic visit rates due to TDI exposure incidents (including both irritant and allergic airway responses) declined from 20.5 to 1.0 visits per 100 years of unit employment. The annual incidence of TDI-induced asthma declined from 1.8% prior to 1980 to 0.7% afterwards. Neither cross-sectional nor longitudinal analyses of FVC and FEV_1 revealed significant dose-response findings relative to TDI exposure across the total exposed population. Among occupational asthma cases there

was an apparent initial decline in FEV_1 within ± 2 years of first reporting symptoms, but not an accelerated rate of decline in follow-up tests from 4 to 30 years after asthma induction.

Conclusions: - Occurrences of both TDI-induced asthma and irritant airway responses due to TDI exposure were observed in this cohort, but no relationship was found between cumulative TDI exposure and irreversible airflow obstruction as assessed by spirometry.

KEY WORDS: toluene diisocyanate, lung function decrement, occupational asthma

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Toluene diisocyanate (TDI) is an important industrial chemical used in the synthesis of a variety of polyurethane products. Although numerous clinical and epidemiological studies have been conducted to assess the effects of TDI exposure on respiratory health, many unanswered questions remain, particularly regarding the effects of long-term low level exposure and the relative importance of peak versus cumulative exposure in inducing adverse outcomes. Asthma occurrence has been evaluated relative to TDI exposure in occupational health clinic settings, through large-scale surveillance programs, and in defined employee populations.[1-10] With few exceptions, reliable exposure data have been lacking to support these investigations. Similarly, lung function decrement has been assessed in a variety of work settings via both cross-sectional and longitudinal studies.[1, 4,11-12] The longitudinal studies are generally of superior design, but those with more detailed assessments of exposure have been of relatively short duration, mostly in the range of 1 to 6 years.

The present study was undertaken to assess the respiratory health of employees of a BASF TDI manufacturing unit that began operations in 1967. Although based on existing surveillance records, our approach was patterned after that employed in a 5-year longitudinal study of another TDI manufacturing unit conducted by researchers at Tulane University.[10,12] Three aspects of respiratory health were evaluated in our study: (1) the nature and occurrence of acute respiratory responses following specific TDI and phosgene exposure incidents, (2) the induction of allergic airway disease and (3) irreversible effects on airflow as measured by spirometry.

METHODS

Study Design: This study was undertaken at a BASF manufacturing complex in Geismar, Louisiana and is based on personnel, industrial hygiene (IH) and on-site occupational health clinic data collected through long-standing medical and IH surveillance programs. TDI unit and referent employees were nested within a larger cohort of 2,133 site employees previously studied for mortality.[13] The study design combined a retrospective cohort approach in identifying participants with a longitudinal assessment of extant medical and exposure records. The objectives and proposed methods were explained to employees and their representatives in a series of meetings before undertaking the study.

Study Group and Referents: The study group included all production and supervisory employees assigned to the TDI unit for 3+ months between its inception in March, 1967 and 06/30/92. The choice of closing date assured that each participant could potentially be followed at least five years after initial assignment to the TDI unit. The study group also included maintenance employees working in the unit between 1977 and 1984. Employees assigned only to clerical or administrative staff positions were not considered eligible for the study.

Internal referents were selected from among all other site employees excluding those ever assigned to either the TDI or a diphenylmethane diisocyanate (MDI) production unit. The referents were frequency-matched by pay status at hire (hourly/nonexempt vs. exempt salary), race, employment date and birth date with one referent selected for every two men in the study group. Referents were selected at random from within the corresponding frequency categories.

Because there were few women employees in the study group, twice the number of women referents were selected. A total of 148 men and 22 women were initially chosen as referents. After review of the medical files, 10 of the 168 selected referents were found to have worked with TDI in production, maintenance or laboratory positions and were shifted to the study group. Thus, 471 employees (313 study group and 158 referents) were included in the study.

Exposure Assessment: - The TDI manufacturing operation consisted of processes to convert dinitrotoluene to toluene diamine (TDA), generate phosgene, convert TDA to the diisocyanate via phosgenation and recover unconsumed phosgene; it included a tank farm and loading operation as well. The processes were run as continuous closed systems. TDI exposure was primarily associated with specific activities such as sample collection, breaking down equipment, removing process residues, and tank car or truck loading. TDI and phosgene were the two key respiratory hazards of interest.

Initial area sampling for TDI began in 1967 using a Uni-Jet TDI-in-air analyzer. Personal sampling based on a paper-tape monitoring method (MCA Company, Model MCM4000 Personal Monitor) was begun in 1976.[14] This method enabled determination of both peak (averaged over a 9-minute sampling period) and 8-hour time-weighted average (TWA) concentrations. Critical reviews of the method are available.[15-16] Starting in 1989, personal sampling for TDI was performed by OSHA Method 42, which uses glass fiber filters coated with 1-(2-pyridyl)piperazine followed by solvent desorption. Samples were analyzed for both 2,4- and 2,6-TDI using high performance liquid chromatography (HPLC).

Area sampling for phosgene was initiated in 1967 using an MSA Universal Tester. Beginning in 1976, personal samples were collected via an MDA Company Model MCM4020/152 Miniature Personal Monitor. Passive dosimeters were used for immediate assessment of phosgene exposures from 1980 forward. The first dosimeter was developed internally using a commercially available tape impregnated with 4(4'-nitrobenzyl)pyridine (MDA Scientific, Inc., Parkridge, IL).[17]

Clinical Data Collection: Each available medical record was reviewed in its entirety and relevant items were extracted from dispensary visit reports and pre-placement and periodic medical examinations by two of the study authors (S.L.P. and M.G.O.). Forty records (8.1%), 16 study group and 24 referents, were not located. Thirty of these records pertained to individuals who had left the company prior to 1980 and 8 others to employees who had transferred to other company locations.

Employee-initiated visits: For exposure-related clinic visits, the following items were abstracted: date of event, chemical substances involved, a description of exposure circumstances, the signs and symptoms reported by the employee and medical treatment rendered, referrals, physician diagnoses, and any recommendations for temporary or permanent removal from the TDI work environment. Qualifying incidents included inhalation exposures regardless of work location and skin or eye contact exposures within the TDI unit.

Occupational asthma case identification: For individuals with asthma-like reactions, we relied primarily on the site physician's assessment of work-relatedness as recorded in the medical

record. That assessment was most often based on symptom history and occasionally included specific IgE determinations, pre- and post-shift lung function testing, and referral to outside pulmonologists. There was no indication that specific inhalation challenge (SIC) tests had ever been used to confirm a diagnosis or that bronchial hyperresponsiveness had been evaluated. Temporary or permanent restriction from the unit was a physician decision. The earliest date, on which symptoms consistent with occupational asthma were reported, was taken to be the onset date for analysis purposes. Generally, the occurrence of a single episode of asthma-like symptoms was not considered sufficient to classify the individual as having occupational asthma.

Pre-placement and periodic examinations: Health examinations offered at hire and periodically thereafter included a health questionnaire, clinical laboratory tests, spirometry and physical examination. A standardized health questionnaire has been used at the site since 1980. Responses to each of four respiratory symptom questions were treated as dichotomous outcome variables. The four questions were: Since your last company health evaluation have you had any of the following? (1) wheezing in chest, (2) cough lasting over 2 months, (3) chest discomfort with exercise/cold weather and (4) shortness of breath when walking.

Cigarette smoking data were extracted from pre-placement and periodic examinations and included year started and stopped smoking and average number of cigarettes smoked per day. Year began smoking was that reported on the earliest available smoking history. Cumulative pack years smoked was calculated as the average number of cigarettes smoked per day times the years of smoking up to the relevant examination date.

Information was collected on asthma and allergy history during both pre-placement and periodic health examinations. Individuals were classified as positive or negative for history of nonoccupational asthma at hire and during employment. The determination of asthma at hire was based on the pre-employment examination and reports of childhood asthma on later periodic examinations. A history of hay fever and allergic reactions to foods, pollens, medicines and injections was similarly abstracted from pre-placement and periodic examination questionnaires. Atopy was not assessed by allergy skin tests.

Spirometric data obtained prior to standardization of the medical examination program in 1980, were judged to be unacceptable because of data quality issues. Consistency in the quality of data improved with the introduction of microprocessor-assisted technology in 1980 (Jones Datamatic Spirometer System, updated in 1989 to a Jones Datamite V System [JONES Medical Instrument Co., Oak Brook, IL]). For this study, hard copy records of all test results including analog graphic output were individually reviewed by the study investigators and evaluated for reproducibility, duration of expiratory effort, interruptions in flow rate, and other indications of unacceptable test results. On occasion, test performance was poor because of current illness or recent surgery. A computer file was developed of test results including the number of trials and any reasons for unacceptable test performance. The reproducibility requirement for both FVC and FEV_1 was agreement of the two best trials within 5% or 0.2 liters. For analysis purposes, the highest FVC and FEV_1 value was chosen and could come from different trials. Expiration efforts of <3 seconds or before a plateau was reached were considered unacceptable for FVC determination.

Based on these quality assurance checks, 3.5% of the spirometry tests were ruled unacceptable because of inadequate test documentation, poor quality of effort, or poor technician performance. These results were not included in subsequent statistical analyses. An additional 10.5% of the tests did not fully meet the reproducibility requirement. Caution is required in excluding such observations because the failure may itself be a measure of "less than perfect health".[18] Within our data set, the reproducibility requirement was less frequently met among individuals over age 60, among heavy cigarette smokers and, in general, among persons with low FVC or FEV_1 values. The requirement was also less often met when 5 or more trials were performed indicating that the technician had recognized the poor reproducibility and initiated further trials. Because of potential selection effects, subsequent statistical analyses were run both including and excluding data not meeting the reproducibility requirement.

Regression analyses were also undertaken to evaluate spirometer effect, technician performance and consistency of results by test date controlling for subject and mean decline in annual lung function decrements. These analyses revealed several technicians whose results deviated from average by up to 0.1 liter and two time periods where results deviated by between 0.1 and 0.2 liters. Again subsequent statistical analyses were run with and without adjustment for technician and time period differences.

Linking IH and Health Data: A job-exposure matrix approach was used to estimate individual TDI exposure. Job-specific work histories were coded for each individual and linked to IH measurements via social security numbers, job category, and date. TWA and peak exposure concentrations were aggregated on a job- and time-specific basis for three job groups of low,

moderate and high potential TDI exposure developed from job descriptions and through reference to a prior TDI unit study.[10] The high potential exposure group was comprised of operators assigned to TDI loading operations. The moderate exposure group consisted of operators performing field operations such as sample collection and removing residues from equipment. The low exposure group included control room operators, supervisory personnel, technicians, and maintenance personnel whose duties involved less frequent direct exposure situations. Regression analyses were then performed to characterize changes in TWA estimates for each job group over time. For individual sampling results reported as "less than" a specified value, one half that value was used in the calculations. Cumulative dose estimates (ppb-months) were computed by multiplying the mean TWA concentration during a particular job assignment by the time spent in that job (expressed in months and fractions thereof) and summing across all job assignments. The mean concentration was the concentration predicted by the regression model for the appropriate job group at the midpoint of that job assignment. Computer algorithms were written so that TWA concentrations and cumulative TDI dose could be estimated for each employee as of any given date.

Methods of Analysis: Computations were performed using the Statistical Analysis System (SAS), Version 6.12 for PCs. Incidence rates were calculated via a person-years approach. Cumulative incidence of occupational asthma was also estimated by the Kaplan-Meier method.[19] Risk factors for TDI-induced asthma and irritant effects were investigated via an instantaneous hazard model approach. For questionnaire responses, relationships between respiratory symptoms and exposure indices were assessed with a repeated measures procedure employing generalized estimating equations (GEEs). The REG procedure in SAS was utilized in

cross-sectional analyses of lung function data. The GEE model within the GENMOD procedure was employed for assessment of longitudinal lung function data.

RESULTS

The duration of TDI unit assignments averaged 5.7 and 4.7 years among men and women employees, respectively, with a range of 3 months to 30 years. The study and referent groups were similar in race (25% vs. 27% black, respectively), percent salaried (8% in both groups), hire year, and age at hire. The higher percentage of women in the referent group (13% vs. 4%) reflects the previously described sampling strategy. Duration of site employment averaged 15.4 years in the study group and 12.2 years among referents.

TDI exposure: - Area sampling in 1967 (N=42) revealed TDI concentrations mostly below 10 ppb; concentrations of 25 ppb were detected in the residue handling area. Between 1969 and 1973, TDI concentrations in the reactor, control room and change house areas were again below 10 ppb, with higher concentrations in the residue handling area. Concentrations of 60 to 80 ppb were measured in the distillation area and during tank truck loading in 1973.

Personal 8-hour samples collected by the paper-tape method from 1976 through 1988 averaged 5.9 ppb TDI (N=156). Eight-hour samples collected by the filter method between 1989 and 1997 averaged 2.8 ppb TDI (N=84). The percentages of 2,4-isomer to total TDI in filter samples ranged from 60 to 70%, with no remarkable differences relative to season or type of sampling

(TWA or task-specific). TWA estimates (mean ± SEM) ranged from 9.9 ± 1.5 ppb TDI in high potential exposure jobs prior to 1985 to < 1.0 ± 0.1 ppb TDI in low potential exposure jobs after 1985 (Figure 1) and averaged 4.2 ppb TDI across all jobs and time periods. Regression analyses showed that TWA estimates declined significantly over time for all job groups. The distributions of cumulative TDI dose and average TDI concentration over an individual's entire work career are provided in Table 1.

Positive associations were observed between TWAs and both the frequency of peak concentrations above 20 ppb (measured by paper tape method) and the rates of TDI-related medical dispensary visits. The frequencies of peak concentrations above 20 ppb were 0.9 and 0.5 per 8-hour shift in high and moderate potential exposure jobs, respectively. Between 1967 and 1996, there were 124 self-initiated dispensary visits attributed to TDI exposure incidents, all in the study group. The TDI exposure incident rates per 100 work-years increased with assignment to higher potential exposure jobs and declined over time in parallel with trends in TWA concentrations. Prior to 1985, there were 20.5, 10.9, and 3.6 TDI-related visits per 100 work-years in the high, moderate, and low potential exposure jobs, respectively. From 1985 forward, the corresponding rates were 4.6, 4.9, and 1.0 incidents per 100 work-years. TDI exposure incidents were reported by 77 different employees and included 58 incidents related to asthmatic or allergic skin reactions in 29 different individuals (19 with asthmatic reactions only, 9 with skin allergies only, and 1 person with both asthma and skin allergies).

There were 46 incidents related to acute TDI inhalation exposures, exclusive of those associated with diisocyanate-induced asthma. Responses ranged from upper airways irritation to a toxic

bronchitis. Transport to an emergency care facility occurred with 10 episodes. Possible risk factors for experiencing an acute TDI inhalation exposure were evaluated via an instantaneous hazard analysis. The analysis was based on determining the total risk set at the time of each event and accumulating evidence across events in favor or against specific associations. The likelihood of an exposure incident was not statistically related to gender, race, history of non-occupational asthma, hay fever or other allergies or current level of cigarette smoking. Significant associations were observed for job category (higher rates for jobs involving either fieldwork or tank car loading), TDI concentration (expressed as a TWA), age, and duration of unit employment (data not shown). Age and duration of unit employment were inversely related to risk, that is, risk was higher for younger individuals and those with fewer years of unit service.

Phosgene exposure: - Phosgene concentrations were mostly below the 0.05 ppm limit of quantification (area samples, 1967-1973). Eight-hour personal samples (N = 42) collected between 1977 and 1988 averaged 0.007 ppm phosgene with a maximum TWA concentration of 0.04 ppm. No significant statistical trends were observed relative to either job category or year of sampling.

There were 176 phosgene exposure incidents between 1967 and 1996, 152 of which were reported by TDI unit employees. Transport to emergency care facilities occurred in 39 instances. Two cases experienced pulmonary edema, one of which resulted in a fatality. Analyses of correlates of cases versus noncases again showed that risk decreased with increasing age and longer total employment. The incident rate during assignment to the TDI unit was 9.5 and 3.4 incidents per 100 work-years before and after 1985, respectively. Highest incident rates were

observed for the field operator job group with 12.7 and 5.6 incidents per 100 work-years at risk, pre- and post-1985. Phosgene badge readings obtained during 20 of the reported exposure incidents revealed concentrations below 2.5 ppm-minutes in 40% of the incidents and between 2.5 and 9.9 ppm-minutes in 35% of the incidents. The remaining readings were above 10 ppm-minutes.

Diisocyanate-induced asthma: The medical record review identified 19 presumed cases of TDI-induced asthma (6.4% of all study group subjects with available medical records). An additional employee developed an MDI-induced asthma following an exposure incident in the MDI unit, but thereafter experienced asthmatic reactions in the presence of very low TDI concentrations. This individual had previously worked in the TDI unit for 5 years without asthmatic symptoms.

Selected characteristics of the 19 TDI-induced asthma cases are summarized in Table 2. In 11 cases, asthmatic symptoms were first reported prior to 1980. Six cases occurred among employees who were part of the initial 1967 TDI unit workforce. Eleven cases held field operator positions and two were assigned to tank car loading at the time of symptom onset. The six remaining cases had been assigned to maintenance (3 cases), plant supervision (1 case), instrumentation (1 case) or laboratory analysis (1 case).

In addition to the cross-sensitization case described above, a second individual reported multiple episodes of asthmatic reactions related to very low level TDI exposures. This employee had remained in the TDI unit for 2+ years after first reporting symptoms. Initially, he experienced a

delayed asthmatic response. Later, he reported an immediate response with symptoms including nasal congestion, wheezing, and thick foamy mucus production. After reassignment he experienced several severe asthmatic episodes associated with very low level TDI concentrations. One episode occurred while attending a training session in a TDI office area.

A conditional logistic regression analysis was performed to evaluate potential risk factors for developing TDI-induced asthma (Table 3). Four factors were statistically related to asthma risk at the 0.05 significance level. These were: (1) prior TDI exposure incident, (2) prior phosgene exposure incident resulting in hospitalization, coughing, chest pain, or difficulty in breathing, (3) current level of cigarette smoking (inversely related to risk), and (4) duration of prior TDI exposure (also inversely related to risk), These findings are based on very small numbers of cases. For example, only 5 of 19 cases had reported prior phosgene exposure incidents, and six had experienced prior TDI exposure incidents. Two of the TDI incidents related to rashes that had developed while handling TDI or waste products containing TDI.

The yearly incidence of TDI-induced asthma cases was 1.1% (19 cases in 1,779 TDI unit work-years), but was higher prior to 1980 (1.8%) than after 1979 (0.7%). The cumulative incidence for individuals assigned to the TDI unit for at least 20 years was estimated by the Kaplan-Meier method to be 11.5% (95% CI: 5.3 – 17.7%).

Medical examination findings: Cigarette smoking and nonoccupational asthma history were available for 87% and 89% of all employees and 97% and 99% of the 395 employees employed at any time after 1979. The percentage of ever cigarette smokers was 68% and 58% within the

study and referent groups, respectively. A higher percentage of referents reported a history of asthma prior to employment (8.5% vs. 2.4%). There were no remarkable differences between the two groups in reporting a history of hay fever (3.9% vs. 4.4%) or other allergies excluding asthma at hire (7.0% vs. 7.2%).

Study and referent employees completed 2,677 periodic questionnaires through mid-1997. Data were not available for the 76 employees who had left active employment before 1980. Between 1 and 18 questionnaires were completed by 363 (92%) of the remaining 395 employees. From 1980 forward, yearly participation in examination program averaged 61% and 60% among referents and exposed employees, respectively.

In Table 4, the results of logistic regression analyses for respiratory symptoms are summarized for four explanatory factors. Positive response percentages ranged from 1.4% (37 of 2,677) for cough lasting 2 months to 5.2% for wheezing in chest. Cigarette smoking was associated with wheezing in chest, cough lasting 2 months, and reporting one or more airways symptoms. History of nonoccupational asthma was associated with wheezing in chest and reporting one or more airways symptoms, but not with chronic cough. A similar symptom pattern was observed for employees with diisocyanate-induced asthma. Among these individuals, most of the questionnaire data (79%) pertained to examinations after restriction from the TDI unit. There was no trend in the percentage of positive responses to wheezing in chest (17%, overall) for pre-exposure versus post-exposure time periods; for the period 5+ years after diagnosis, the positive response rate for wheezing in chest was 16%. Three cases reported routine use of asthma medications after assignment to other work areas. No significant associations with questionnaire

responses were observed for TDI exposed vs. referents either in analyses with or without diisocyanate-induced asthma status included as a covariate. When both nonoccupational and occupational asthma cases were removed from the analyses, there were again no significant differences between the exposed and referent groups.

Spirometry: - One or more lung function tests were available for 371 (94%) of 395 employees employed on or after January 1, 1980. The average number of tests per employee was 7.5 and the average interval between the earliest and most recent test was 9.3 years.

An initial cross-sectional analysis was carried out using the earliest available lung function test to determine if prior TDI exposure was associated with FVC, FEV_1 and FEV_1/FVC% (data not shown). The average age of employees at the time of testing was 35.6 years. The mean TDI dose was 148 ppb-months with a range up to 983 ppb-months. TDI dose was forced into the model with other factors selected by backward elimination using a 0.05 significance level. These factors included age, height, race, gender, cigarette pack years, TDI concentration (TWA), history of non-occupational asthma, history of allergies except asthma, prior phosgene exposure incident with symptoms, and, finally, prior determination of diisocyanate-induced asthma. Age, height, race and gender were significant predictors of FVC and FEV_1. Both cigarette pack years and a prior history of non-occupational asthma were significant explanatory factors for FEV_1 and FEV_1/FVC%, but not for FVC. Neither TDI concentration nor cumulative dose was statistically related to any of the three lung function parameters. Analyses restricted to observations meeting

the reproducibility requirement and adjusted for technician and time period effects yielded the same nonsignificant results relative to TDI concentration and cumulative dose.

Identical cross-sectional analyses were carried out using the most recent lung function test (Table 5). Mean TDI dose had increased to 234 ppb-months and average age to 44.8 years. Age, height, race and gender were significant predictors of FVC and FEV_1 as before and pack years smoked, which had increased to an average of 14.3 pack years, was a significant risk factor for FVC, FEV_1, and FEV_1/FVC%. A prior history of non-occupational asthma remained a statistically significant predictor of FEV_1 and FEV_1/FVC%. The occurrence of prior phosgene exposure incidents was associated with declines in both FVC and FEV_1 and occupational asthma was associated with a decline in FEV_1/FVC%. TDI concentration and cumulative dose were not significant predictive factors in the full model or in models without occupational asthma status as a covariate. The same results were obtained in the restricted analyses. An additional set of analyses carried out for 119 never smokers also found no statistical relationship between spirometry outcome and either TDI concentration or dose (data not shown).

Longitudinal analyses (Table 6) were performed to estimate the annual change in FVC and FEV_1 for various population subgroups with 3+ lung function tests covering an interval of 2+ years. For men the average annual decline in FVC and FEV_1 was 0.036 and 0.037 liters/year, respectively and for women employees the average annual declines were 0.019 and 0.023 liters/year. FVC and FEV_1 declines were greater among cigarette smokers than never smokers. The annual decrements in FVC and FEV_1 among individuals with a prior history of non-

occupational or occupational asthma were unremarkable; however, baseline FEV_1 was lower by about 0.3 liters for both subgroups relative to that of other men in the study.

Differences in annual FVC and FEV_1 decrements between exposed and referent groups were evaluated by including exposure status as an explanatory factor for slope in the regression model. Separate analyses were performed for men and women employees and for men who never smoked cigarettes and those who accumulated 20+ pack years of cigarette smoking. Among men, annual FVC and FEV_1 decrements were not statistically associated with exposure status, consistent with the small slope differences between exposed and referents reported in Table 6. Among women, there was a statistical difference ($p = 0.03$) between exposed and referent women in the rate of FEV_1 decline. This finding is based on observations for only 10 exposed (average decrement: 0.027 liters/year) and 12 referent women (average decrement: 0.014 liters/year). Average pack years smoked was much higher among TDI-exposed women than referents (14.8 vs. 4.6 pack years) and follow-up interval was nearly five years longer among women in the TDI group.

Additional modeling of factors potentially influencing annual FVC and FEV_1 decrements is summarized in Table 7 for the total population and individuals who never smoked cigarettes. In general, the annual rate of decline in FVC and FEV_1 was less among women and blacks. Among nonsmokers the rate of decline in FVC and FEV_1 accelerated with increasing age. For the total population, FVC and, in particular, FEV_1 decrements accelerated with increased pack years smoked. Relative change in Body-Mass-Index (BMI) was also an important predictive factor for

change in the rate of FVC decline and, to a lesser extent, was related to change in the rate of FEV_1 decline. Cumulative TDI dose was not significantly related to the annual decline in either FVC or FEV_1. Analyses restricted to individuals with at least 5 spirometry tests and tracings meeting all quality assurance requirements yielded the same results for TDI dose; p-values were marginally different for some of the remaining covariates (data not shown).

Lung function data were also evaluated for 18 individuals who developed diisocyanate-induced asthma. For 8 individuals, with data available prior to first reported asthma symptoms, FEV_1 values averaged 0.03 liters below expectation. Among 5 individuals tested while working in the unit and within 2 years of first reporting asthmatic symptoms, FEV_1 averaged 0.44 liters below expectation. Similar results were observed for individuals who remained in the unit for up to 2 years after symptoms were reported. Individual data points for FEV_1 before, during, and after TDI exposure are plotted in Figure 2. On average, the interval between date of initial asthma symptoms and the most recent lung function test was 13.8 years (range of 4 to 30 years). Most cases were reassigned to other work areas within a year of reporting asthmatic symptoms, but remained employees of the company.

DISCUSSION

Nineteen cases of presumed TDI-induced asthma (6.4%) were identified over a 30-year observation period in this cohort. Because cases were not confirmed by SIC, it is possible that overascertainment occurred. In one recent study of 114 isocyanate workers referred for evaluation of respiratory complaints,[20] 46 were found to have a work-related pattern of asthma symptoms, but only 14 of these men could be confirmed to have occupational asthma by SIC. Thirty of the 46 workers had positive methacholine challenge tests.[20] In a second study, SIC-proven asthma was confirmed in only 41% of TDI-exposed workers referred because of probable occupational asthma.[21] Among individuals with positive SIC, 78% had positive methacholine responses; however, among individuals with negative SIC, 46% were positive by the methacholine challenge test. Thus, differentiation between individuals with bronchial hyperresponsiveness and those with SIC-proven occupational asthma could be difficult when relying on history alone. Because the total at-risk population was not studied, it cannot be determined from these referral studies whether or not bronchial hyperresponsiveness is itself an outcome of long-term TDI exposure. However, Jones *et al* had not observed a relationship between TDI exposure and methacholine challenge test results among persons employed in the polyurethane foam industry.[4]

True cases could have been missed as we relied on self-reporting of symptom histories and employee may have left the TDI unit without reporting symptoms to the health clinic or may have been reassigned on a precautionary basis. Additionally, there may have been insufficient detail in the medical records to enable case status to be accurately determined.

Underascertainment is less likely among long-term unit employees because asthmatic individuals who continue to work in exposure areas often develop increasingly severe symptoms.

The annual incidence of TDI-induced asthma observed in our study (ranging between 0.7% and 1.8%) was comparable to that seen in other similar investigations in a TDI manufacturing facility[10] and in polyurethane foam operations,[4] where TDI concentrations were in the same range as the present study. Our study most closely parallels the Tulane study.[10,12] During comparable observation periods in the mid- to late-1970s, TWA estimates for TDI were somewhat higher for the Geismar unit. Since then, TDI concentrations have declined steadily in our unit. Twelve of 277 employees (4.3%) included in the Tulane study became clinically "sensitive";[10] nine cases developed within one year of first exposure and six cases had been subject to high short-term exposures during TDI spills. No mention was made of acute exposures to other respiratory irritants.

In our study, cases also tended to occur among newly recruited employees and to be associated with prior TDI exposure incidents (6 cases). In addition, cases were linked to prior acute phosgene exposure incidents (5 cases). The phosgene finding could be a chance occurrence. It might also be that a disproportionate share of individuals, who experienced respiratory symptoms following phosgene exposure, had pre-existing bronchial hyperresponsiveness or that the exposure incident induced bronchial hyperresponsiveness or other respiratory tract changes that increased the likelihood of developing asthmatic responses during TDI exposure. Acute chlorine exposures resulting in severe respiratory symptoms have been observed to produce both

transient increases in bronchial hyperresponsiveness and transient decreases in airway function.[22] Because our asthma cases were diagnosed by symptom history and were not confirmed by SIC, the case group may include individuals with underlying bronchial hyperresponsiveness but not immunologically-mediated asthma. Such a selection mechanism might also partly explain why potential diisocyanate-induced asthma cases referred to specialty clinics[20-21] frequently test positive on methacholine challenge, but negative on SIC.

In both cross-sectional and longitudinal analyses covering an 18-year observation period, we found no convincing evidence linking lung function decrement to cumulative dose or average TDI concentration. For a subset of individuals determined to have diisocyanate-induced asthma, there was a significant decline in the average FEV_1/FVC% as of their most recent test. A relative decline in FEV_1 had been noted among cases actively working in exposure areas and tested within ± 2 years of first reporting asthmatic symptoms. Longitudinal analysis of FVC and FEV_1 trends among occupational asthma cases was unremarkable; the average annual FEV_1 decrement of 0.038 liters/year was the same as the average decrement among all study participants.

In the Tulane study, cumulative dose treated as a continuous variable was also not significantly related to annual FVC or FEV_1 decrements.[10] However, a significant effect on the rate of FEV_1 decrement was seen using a dichotomous dose measure (TDI dose above vs. below 68 ppb-months) with a larger relative decrement observed for never cigarette smokers.[10] In our study,

subanalyses restricted to never cigarette smokers did not reveal significant trends in annual FVC or FEV_1 decrements relative to TDI dose.

As our lung function testing program was not carried out as part of a research effort and in true prospective modality, there was undoubtedly less tight control over data quality than might have been the case otherwise. However, all individual data were audited and the analysis findings were robust with respect to the reproducibility requirement and adjustments for technician and time period effects. Furthermore, our estimates of the effects of various covariates on lung function appear to be consistent with findings in the literature. For example, in a cross-sectional analysis of never smokers, the estimated age effect on FEV_1 of –0.026 liters per year was in the midrange of predicted values (–0.021 to –0.032 liters).[18] Our longitudinally-based estimates of annual change in FEV_1 of –0.037 and –0.023 liters/yr for men and women, respectively, are in agreement with estimates of -0.035 and -0.024 liters/yr in asymptomatic nonsmoking men and women from a general population for comparable age categories.[23] The effect of pack years smoked on FEV_1 and FEV_1/FVC% was also readily detectable in both our cross-sectional and longitudinal analyses. Finally, we detected effects of weight gain on longitudinal changes in FVC and FEV_1 comparable to those reported by Wang *et al*[24] and observed declines in FEV_1 among asthmatics, but of a lesser magnitude than reported by Lange *et al*[25].

The lack of lung function tests prior to 1980 is a concern because TDI exposures were known to have been higher before than after that date. Of the 190 employees with TDI unit assignments

prior to 1980, 39 had left active employment by 1980. It is not known whether or not this group of former employees differentially included individuals whose respiratory health was impacted by exposure. However, lung function analyses, that included 145 of the remaining 151 individuals exposed during that time period, demonstrated no relationship between cumulative exposure and either FVC or FEV_1. Additionally, review of mortality follow-up through 1992 for the total Geismar cohort[13] did not identify any respiratory disease deaths among TDI unit employees who had terminated employment prior to 1980. Review of employment records also did not provide evidence of employment termination due to poor respiratory health.

An additional consideration is that, in past years, there may have been reluctance to assign employees to the TDI unit who had pre-existing respiratory conditions. A history of non-occupational asthma, mostly noted as childhood asthma, was reported by 8.3% of the referents and only 2.5% of the TDI unit employees with spirometry data. Also, the mean FVC and FEV_1 determinations were about 0.2 liters lower in referents than TDI unit employees at baseline. There was no notable difference in pack years smoked between the two groups except that cigarette smoking was more common among exposed than referent women. Because there was no evidence of a TDI dose-response relationship based on final FVC and FEV_1 determinations and no relationship between annual decrements in FVC or FEV_1 and TDI dose, it is unlikely that initial selection effects would have obscured irreversible lung function effects related to TDI exposure.

In summary, this study provides cross-sectional and longitudinal lung function data for TDI-exposed individuals over a longer time frame than was previously available. In agreement with other studies conducted in workplaces with exposures ranging up to 5 ppb TWA and where active medical surveillance and exposure monitoring programs were in place,[4,10,26-27] we found little evidence of a relationship between TDI exposure and either FVC or FEV_1 decrement. Routine medical surveillance is recommended to assure early detection and evaluation of individuals experiencing asthmatic reactions to diisocyanates.

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Table 1. Distribution of cumulative dose and TDI concentration averaged over entire exposure period for 313 study group employees, 1967-1996.

Exposure Measure	Number	Percent
Cumulative TDI dose (ppb-months)		
< 50 ppb-months	47	15.0%
50 – 99 ppb-months	62	19.8%
100 – 199 ppb-months	98	31.3%
200 – 499 ppb-months	73	23.3%
500+ ppb-months	33	10.5%
Average TDI concentration across all TDI unit job assignments		
< 1.0 ppb	13	4.2%
1.0 – 2.9 ppb	113	36.1%
3.0 - 4.9 ppb	59	18.8%
5.0 - 6.9 ppb	94	30.0%
7.0+ ppb	34	10.9%

Table 2. Description of 19 presumed TDI-induced asthma cases.

Host and Exposure Parameters	Symptom onset	
	Prior to 1980	1980 +
Gender		
men	11	6
women	0	2
Job category		
field operator	6	5
maintenance/technician	3	2
TDI loading	2	0
supervisor	0	1
Cigarette smoking status		
nonsmoker	9	5
current: <1 pk/day	1	0
current: 1+ pk/day	0	3
unknown	1	0
Basis for case ascertainment		
sympt hx	10	3
sympt hx + pulmonologist evaluation	1	2
sympt hx + pre/post shift PFTs	0	3
Prior TDI/phosgene exposure incident		
none	8	2
TDI	1	3
Phosgene	0	2
Phosgene and TDI	2	1
Duration of prior TDI exposure		
2 – 11 months	5	2
12 – 35 months	4	3
36 – 59 months	1	2
60 + months	1	1
Duration of exposure after symptom onset		
< 0.5 years	8	4
0.5 – 0.9 years	1	3
1.0 – 1.9 years	1	1
2.0 + years	1	0

Table 3. Risk factors for developing presumed TDI-induced asthma (analysis based on conditional logistic regression using backward elimination).

Explanatory Variables [1]	Risk Ratio	95% CI
Prior TDI exposure incident (Y=1, N=0)	3.1	1.1-9.0
Prior phosgene exposure incident (Y=1, N=0)	4.3	1.3-15.7
Current cigarette smoking (# pks/day)	0.4	0.1-1.0
Duration of exposure (years)	0.8	0.7-0.9

[1] Three parameters, TDI exposure intensity (8-hr TWA), prior inhalation exposure to any respiratory irritant other than TDI and gender were not significant at the 0.05 level.

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Table 4. **Explanatory factors for selected respiratory symptoms reported over 18-year period among TDI-exposed and referent employees (Multivariate logistic regression model, generalized estimating equation approach).**

Respiratory symptom and covariate[1]	Risk Ratio (RR)	95% Confidence Interval (CI)
Wheezing in chest (138 positives)		
Packs of cigarettes smoked daily	3.4	2.0 – 5.7
Hx of nonoccupational asthma	3.4	1.5 – 8.0
Positive for TDI-induced asthma	8.8	4.0 – 19.4
TDI Exposed vs. Referent Group	0.8	0.4 – 1.5
Cough lasting 2 months (37 positives)		
Packs of cigarettes smoked daily	2.2	1.3 – 3.7
Hx of nonoccupational asthma	0.7	0.1 – 3.3
Positive for TDI-induced asthma	0.8	0.1 – 5.5
TDI Exposed vs. Referent Group	0.9	0.4 – 2.2
Chest pain on exercise (63 positives)		
Packs of cigarettes smoked daily	1.0	0.5 – 2.0
Hx of nonoccupational asthma	2.9	0.5 – 14.9
Positive for TDI-induced asthma	4.2	1.6 – 10.7
TDI Exposed vs. Referent Group	0.7	0.3 – 1.9
Shortness of breath (59 positives)		
Packs of cigarettes smoked daily	1.4	0.8 – 2.3
Hx of nonoccupational asthma	1.6	0.5 – 5.6
Positive for TDI-induced asthma	1.7	0.6 – 4.8
TDI Exposed vs. Referent Group	1.1	0.5 – 2.4
One or more symptoms (232 positives)		
Packs of cigarettes smoked daily	2.4	1.6 – 3.6
Hx of nonoccupational asthma	3.0	1.3 – 6.7
Positive for TDI-induced asthma	4.2	2.1 – 8.4
TDI Exposed vs. Referent Group	0.8	0.4 – 1.3

[1] Based on 2,677 periodic examinations, gender included as covariate (data not shown)

Table 5. Regression of FVC, FEV_1 and FEV_1/FVC% on selected explanatory factors based on most recent spirometry test for 371 employees.

Explanatory Factor		FVC		FEV_1		FEV_1/FVC	
Parameter	Mean	β	SE	β	SE	β	SE
Occupational factors							
TDI Dose (ppb-months) [1]	234.2 [2]	0.00009	0.00013	0.00013	0.00011	0.00001	0.000014
Acute Phosgene Exp. (% pos)	11.3%	-0.257**	0.0938	-0.241**	0.0809	-	-
Occupational Asthma (% pos)	4.6%	-	-	-	-	-0.042**	0.0157
Non-occupational factors							
Age (yrs)	44.8	-0.029***	0.0031	-0.030***	0.0027	-0.002***	0.0003
Height (cm)	177.1	0.054***	0.0044	0.040***	0.0038	-0.001*	0.0005
Race (% black)	28.6%	-0.681***	0.0650	-0.485***	0.0560	-	-
Gender (% women)	6.7%	-0.451***	0.1271	-0.364***	0.1097	-	-
Cigarettes (pack years)	14.3	-0.004*	0.0017	-0.006***	0.0014	-0.001***	0.0002
Non-occ. Asthma Hx (% pos)	6.2%	-	-	-0.260*	0.1046	-0.063***	0.0136

[1] TDI dose forced into model, other factors included based on backward selection using 0.05 significance level.

[2] Mean dose in 267 TDI unit employees.

*p<0.05; **p<0.01; ***p<0.001

Table 6. Estimated annual change in FVC and FEV_1 in selected population subgroups based on generalized estimating equation (GEE) analysis approach.

Population Subgroup	Persons #	PFTs #	FVC Baseline (liters)	FVC Slope (liters/yr) estimate (95% CI)	FEV_1 Baseline (liters)	FEV_1 Slope (liters/yr) estimate (95% CI)
Total Group	296	2,641	4.68	-0.035 (-0.031, -0.039)	3.76	-0.036 (-0.033, -0.039)
Women	22	169	3.58	-0.019[NC] (-0.011, -0.026)	2.97	-0.023 (-0.017, -0.029)
Exposed	10	88	3.62	-0.020[NC] (-0.016, -0.024)	3.07	-0.027 (-0.022, -0.032)
Referents	12	81	3.55	-0.014 (0.004, -0.033)	2.89	-0.014 (-0.006, -0.022)
Men	274	2,472	4.77	-0.036 (-0.032, -0.040)	3.82	-0.037 (-0.033, -0.040)
Exposed	209	1,866	4.83	-0.037 (-0.033, -0.042)	3.87	-0.037 (-0.033, -0.041)
Referents	65	606	4.59	-0.034 (-0.027, -0.041)	3.67	-0.035 (-0.028, -0.042)
Men, Never Smokers	92	862	4.76	-0.033 (-0.026, -0.041)	3.85	-0.033 (-0.027, -0.039)
Exposed	67	620	4.82	-0.033[NC] (-0.024, -0.041)	3.89	-0.031[NC] (-0.024, -0.039)
Referents	25	242	4.62	-0.034[NC] (-0.022, -0.047)	3.74	-0.036[NC] (-0.028, -0.043)
Men (20+ cigarette pack yrs)	96	855	4.60	-0.043 (-0.037, -0.049)	3.59	-0.044 (-0.039, -0.049)
Exposed	72	637	4.70	-0.044 (-0.036, -0.053)	3.70	-0.043 (-0.038, -0.049)
Referents	24	218	4.29	-0.041 (-0.031, -0.051)	3.28	-0.044 (-0.034, -0.055)
Men with non-occ. asthma	19	184	4.58	-0.028 (-0.011, -0.046)	3.49	-0.031[NC] (-0.017, -0.044)
Men with occ. asthma	15	142	4.70	-0.037 (-0.026, -0.049)	3.58	-0.034 (-0.023, -0.045)

[NC] nonconvergence of GEE estimates after 50 iterations

Table 7. Linear regression of factors modifying annual change in FVC and FEV_1, analysis based on generalized estimating equation approach among 296 exposed and referent employees.

Population subgroup and explanatory factors	FVC (liters/yr)		FEV_1 (liters/yr)	
	estimate	(95% CI)	estimate	(95% CI)
Total group (N = 296)				
slope	-0.043***	(-0.030, -0.056)	-0.043***	(-0.031, -0.056)
slope*gender	0.018***	(0.008, 0.029)	0.012*	(0.001, 0.022)
slope*race	0.005	(-0.003, 0.012)	0.008**	(0.002, 0.014)
slope*pkyrs	-0.0003**	(-0.0001, -0.0005)	-0.0003***	(-0.0001, -0.0004)
slope*BMI	-0.037***	(-0.019, -0.054)	-0.024**	(-0.008, -0.040)
slope*TDI dose	-0.00001	(-0.00002, 0.00001)	0.00000	(-0.00001, 0.00001)
Never cigarette smokers (N = 101)				
slope	-0.031**	(-0.008, -0.055)	-0.028*	(-0.006, -0.051)
slope*gender	0.020*	(0.003, 0.037)	0.011	(-0.005, 0.028)
slope*race	0.006	(-0.005, 0.017)	0.004	(-0.006, 0.014)
slope*age	-0.0012***	(-0.0005, -0.0019)	-0.0011***	(-0.0005, -0.0018)
slope*BMI	-0.055***	(-0.022, -0.087)	-0.030	(-0.063, 0.003)
slope*TDI dose	-0.00002	(-0.00004, 0.00000)	-0.00000	(-0.00003, 0.00001)

Factor definitions: gender = 1 if woman, else gender = 0; race = 1 if black, else race = 0;
age = (age – 40 years) at last examination; pkyrs = number of cigarette pack years at last examination;
BMI = average annual gain in BMI (kg/m^2) between first and last examination;
TDI dose = cumulative TDI dose in ppb-months at last examination.

$p<0.05$; ** $p<0.01$; *** $p<0.001$

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